Clinical trial results:
A randomized, double-blind, placebo-controlled phase III study of regorafenib plus best supportive care versus placebo plus best supportive care for patients with metastatic and/or unresectable gastrointestinal stromal tumors (GIST) whose disease has progressed despite prior treatments with at least imatinib and sunitinib

Summary

EudraCT number	2009-017957-37
Trial protocol	BE FI NL DE GB AT FR ES IT
Global end of trial date	26 April 2019

Results information

Result version number	v1 (current)
This version publication date	23 April 2020
First version publication date	23 April 2020

Trial information

Trial identification

Sponsor protocol code	14874

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01271712
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Bayer AG
Sponsor organisation address	Kaiser-Wilhelm-Allee, Leverkusen, Germany, D-51368
Public contact	Therapeutic Area Head, Bayer AG, clinical-trials-contact@bayer.com
Scientific contact	Therapeutic Area Head, Bayer AG, clinical-trials-contact@bayer.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	09 May 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	26 April 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Primary: To compare the treatment groups in terms of Progression-Free Survival (PFS), per blinded central radiology review, according to modified Response Evaluation Criteria in Solid Tumors (RECIST) criteria (version 1.1).
Secondary: To compare the regorafenib and placebo treatment groups in terms of overall survival (OS), time to progression (TTP), disease control rate (DCR), tumor response rate (RR), duration of response (DOR), and safety of regorafenib.

Protection of trial subjects:

The conduct of this clinical study met all local legal and regulatory requirements. The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and the International Conference on Harmonization guideline E6: Good Clinical Practice. Before entering the study, the informed consent form was read by and explained to all subjects. Participating subjects signed informed consent form and could withdraw from the study at any time without any disadvantage and without having to provide a reason for this decision. Only investigators qualified by training and experience were selected as appropriate experts to investigate the study drug.

Background therapy:

Best supportive care (BSC)

Evidence for comparator: -

Actual start date of recruitment	04 January 2011
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	8 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	China: 11
Country: Number of subjects enrolled	Japan: 17
Country: Number of subjects enrolled	Singapore: 3
Country: Number of subjects enrolled	Korea, Republic of: 16
Country: Number of subjects enrolled	Austria: 2
Country: Number of subjects enrolled	Belgium: 6
Country: Number of subjects enrolled	Canada: 10
Country: Number of subjects enrolled	Finland: 1
Country: Number of subjects enrolled	France: 19
Country: Number of subjects enrolled	Germany: 32
Country: Number of subjects enrolled	Israel: 1

Country: Number of subjects enrolled	Italy: 20
Country: Number of subjects enrolled	Netherlands: 10
Country: Number of subjects enrolled	Poland: 10
Country: Number of subjects enrolled	Spain: 4
Country: Number of subjects enrolled	United Kingdom: 11
Country: Number of subjects enrolled	United States: 26
Worldwide total number of subjects	199
EEA total number of subjects	115

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	136
From 65 to 84 years	62
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

A total of 240 participants with metastatic and/or unresectable GIST whose disease had progressed despite prior treatments with at least imatinib and sunitinib were screened; 199 were randomized. Patients must have shown objective disease progression or intolerance to imatinib, as well as disease progression while on sunitinib treatment.

Pre-assignment

Screening details:

Participants were randomized in a 2:1 ratio to receive either regorafenib (133 patients) or placebo (66 patients). Randomization was stratified according 3rd vs. 4th line of therapy (at least 50% of patients were to be 3rd line), and geographical region (Asia vs.rest of world).

Period 1

Period 1 title	Double blind treatment
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Monitor, Carer, Subject, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Regorafenib (Stivarga, BAY73-4506)

Arm description:

Participants received Regorafenib (Stivarga) 160 mg (4 x 40 mg tablets) per os once daily, 3 weeks on therapy followed by 1 week off therapy to comprise a cycle of 4 weeks

Arm type	Experimental
Investigational medicinal product name	Regorafenib
Investigational medicinal product code	BAY73-4506
Other name	Stivarga
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

The 40 mg tablets was administered orally, in the morning with approximately 8 fluid ounces (240 mL) of water after a low-fat (< 30% fat) breakfast.

Arm title	Placebo

Arm description:

Double blind phase: Participants received matching Placebo tablets per os once daily, 3 weeks on therapy followed by 1 week off therapy to comprise a cycle of 4 weeks

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

The regorafenib-matching placebo tablets was administered orally, in the morning with approximately 8 fluid ounces (240 mL) of water after a low-fat (< 30% fat) breakfast.

Number of subjects in period 1	Regorafenib (Stivarga, BAY73-4506)	Placebo
Started	133	66
Participants Received Treatment	132	66
Completed	91	58
Not completed	42	8
Adverse event, serious fatal	2	-
Consent withdrawn by subject	4	1
Adverse event, non-fatal	9	4
receive no study drug	1	-
Progressive disease	23	3
Non compliance with study drug	2	-
Lack of efficacy	1	-

Period 2

Period 2 title	Open label treatment
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	No
Arm title	Regorafenib (Stivarga, BAY73-4506)

Arm description:

Participants received Regorafenib (Stivarga) 160 mg (4 x 40 mg tablets) per os once daily, 3 weeks on therapy followed by 1 week off therapy to comprise a cycle of 4 weeks

Arm type	Experimental
Investigational medicinal product name	Regorafenib
Investigational medicinal product code	BAY73-4506
Other name	Stivarga
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

The 40 mg tablets was administered orally, in the morning with approximately 8 fluid ounces (240 mL) of water after a low-fat (< 30% fat) breakfast.

Arm title	Placebo first, then Option of Open Label Regorafenib Treatment

Arm description:

Open Label phase: Participants on placebo who switched to Regorafenib, received Regorafenib 160 mg (4 x 40 mg tablets) per os once daily, 3 weeks on therapy followed by 1 week off therapy to comprise a cycle of 4 weeks.

Arm type	Experimental

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

The regorafenib-matching placebo tablets was administered orally, in the morning with approximately 8 fluid ounces (240 mL) of water after a low-fat (< 30% fat) breakfast.

Number of subjects in period 2	Regorafenib (Stivarga, BAY73-4506)	Placebo first, then Option of Open Label Regorafenib Treatment
Started	91	58
Completed	0	0
Not completed	91	58
Adverse event, serious fatal	6	5
Consent withdrawn by subject	6	11
Physician decision	2	-
Adverse event, non-fatal	14	8
transferred to rollover study	1	-
Non-compliance with study drug	1	-
Switching to other therapy	2	1
Progressive disease	59	32
Protocol deviation	-	1

Period 3

Period 3 title	Safety follow-up
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	No
Arm title	Regorafenib (Stivarga, BAY73-4506)

Arm description:

Participants received Regorafenib (Stivarga) 160 mg (4 x 40 mg tablets) per os once daily, 3 weeks on therapy followed by 1 week off therapy to comprise a cycle of 4 weeks

Arm type	Experimental

Investigational medicinal product name	Regorafenib
Investigational medicinal product code	BAY73-4506
Other name	Stivarga
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

The 40 mg tablets was administered orally, in the morning with approximately 8 fluid ounces (240 mL) of water after a low-fat (< 30% fat) breakfast.

Arm title	Placebo first, then Option of Open Label Regorafenib Treatment

Arm description:

Double blind phase: participants received matching Placebo tablets per os once daily, 3 weeks on therapy followed by 1 week off therapy to comprise a cycle of 4 weeks. Open Label phase: participants on placebo who switched to Regorafenib, received Regorafenib 160 mg (4 x 40 mg tablets) per os once daily, 3 weeks on therapy followed by 1 week off therapy to comprise a cycle of 4 weeks.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

The regorafenib-matching placebo tablets was administered orally, in the morning with approximately 8 fluid ounces (240 mL) of water after a low-fat (< 30% fat) breakfast.

Number of subjects in period 3	Regorafenib (Stivarga, BAY73-4506)	Placebo first, then Option of Open Label Regorafenib Treatment
Started	118	52
Completed	97	37
Not completed	21	15
Adverse event, serious fatal	11	7
Consent withdrawn by subject	4	2
Not analyzed after cutoff 08Jun2015	3	4
No follow-up	1	1
Progressive disease	1	-
Protocol deviation	1	1

Period 4

Period 4 title	Survival Follow-up
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Regorafenib (Stivarga, BAY73-4506)

Arm description:

Participants received Regorafenib (Stivarga) 160 mg (4 x 40 mg tablets) per os once daily, 3 weeks on therapy followed by 1 week off therapy to comprise a cycle of 4 weeks

Arm type	Experimental
Investigational medicinal product name	Regorafenib
Investigational medicinal product code	BAY73-4506
Other name	Stivarga
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

The 40 mg tablets was administered orally, in the morning with approximately 8 fluid ounces (240 mL) of water after a low-fat (< 30% fat) breakfast.

Arm title	Placebo first, then Option of Open Label Regorafenib Treatment

Arm description:

Double blind phase: participants received matching Placebo tablets per os once daily, 3 weeks on therapy followed by 1 week off therapy to comprise a cycle of 4 weeks. Open Label phase: participants on placebo who switched to Regorafenib, received Regorafenib 160 mg (4 x 40 mg tablets) per os once daily, 3 weeks on therapy followed by 1 week off therapy to comprise a cycle of 4 weeks.

Arm type	Experimental
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

The regorafenib-matching placebo tablets was administered orally, in the morning with approximately 8 fluid ounces (240 mL) of water after a low-fat (< 30% fat) breakfast.

Number of subjects in period 4	Regorafenib (Stivarga, BAY73-4506)	Placebo first, then Option of Open Label Regorafenib Treatment
Started	100	39
Completed	85	33
Not completed	15	6
Not analyzed after cutoff 08Jun2015	15	6

Baseline characteristics

Reporting groups	
Reporting group title	Regorafenib (Stivarga, BAY73-4506)
Reporting group description:	
Participants received Regorafenib (Stivarga) 160 mg (4 x 40 mg tablets) per os once daily, 3 weeks on therapy followed by 1 week off therapy to comprise a cycle of 4 weeks	
Reporting group title	Placebo
Reporting group description:	
Double blind phase: Participants received matching Placebo tablets per os once daily, 3 weeks on therapy followed by 1 week off therapy to comprise a cycle of 4 weeks	

Reporting group values	Regorafenib (Stivarga, BAY73-4506)	Placebo	Total
Number of subjects	133	66	199
Age categorical Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			0
Newborns (0-27 days)			0
Infants and toddlers (28 days-23 months)			0
Children (2-11 years)			0
Adolescents (12-17 years)			0
Adults (18-64 years)			0
From 65-84 years			0
85 years and over			0
Age Continuous Units: Years			
arithmetic mean	58.2	58.1	
standard deviation	± 12.5	± 13.9	-
Sex: Female, Male Units:			
Female	48	24	72
Male	85	42	127
ECOG Performance Status (PS)]			
ECOG = Eastern cooperative oncology group PS levels are 0 (Fully active, able to carry on all pre-disease performance), 1 (ambulatory and able to carry out work of a light or sedentary), 2 (Ambulatory and capable of all selfcare but unable to carry out any work activities), 3 (Capable of only limited selfcare, confined to bed or chair more than 50% of awake time), 4 (Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair) and 5 (death).			
Units: Subjects			
PS 0	73	37	110
PS 1	60	29	89
PS 2	0	0	0
Missing	0	0	0
Prior anti-cancer drug group			
3rd line: 3rd in sequence of multiple therapies: imatinib (1st); sunitinib (2nd). 4th line and beyond: 4th in sequence of multiple therapies: imatinib (1st); sunitinib (2nd); other (3rd).			
Units: Subjects			

3rd line	74	39	113
4th line and beyond	59	27	86

End points

End points reporting groups

Reporting group title	Regorafenib (Stivarga, BAY73-4506)
Reporting group description:	
Participants received Regorafenib (Stivarga) 160 mg (4 x 40 mg tablets) per os once daily, 3 weeks on therapy followed by 1 week off therapy to comprise a cycle of 4 weeks	
Reporting group title	Placebo
Reporting group description:	
Double blind phase: Participants received matching Placebo tablets per os once daily, 3 weeks on therapy followed by 1 week off therapy to comprise a cycle of 4 weeks	
Reporting group title	Regorafenib (Stivarga, BAY73-4506)
Reporting group description:	
Participants received Regorafenib (Stivarga) 160 mg (4 x 40 mg tablets) per os once daily, 3 weeks on therapy followed by 1 week off therapy to comprise a cycle of 4 weeks	
Reporting group title	Placebo first, then Option of Open Label Regorafenib Treatment
Reporting group description:	
Open Label phase: Participants on placebo who switched to Regorafenib, received Regorafenib 160 mg (4 x 40 mg tablets) per os once daily, 3 weeks on therapy followed by 1 week off therapy to comprise a cycle of 4 weeks.	
Reporting group title	Regorafenib (Stivarga, BAY73-4506)
Reporting group description:	
Participants received Regorafenib (Stivarga) 160 mg (4 x 40 mg tablets) per os once daily, 3 weeks on therapy followed by 1 week off therapy to comprise a cycle of 4 weeks	
Reporting group title	Placebo first, then Option of Open Label Regorafenib Treatment
Reporting group description:	
Double blind phase: participants received matching Placebo tablets per os once daily, 3 weeks on therapy followed by 1 week off therapy to comprise a cycle of 4 weeks. Open Label phase: participants on placebo who switched to Regorafenib, received Regorafenib 160 mg (4 x 40 mg tablets) per os once daily, 3 weeks on therapy followed by 1 week off therapy to comprise a cycle of 4 weeks.	
Reporting group title	Regorafenib (Stivarga, BAY73-4506)
Reporting group description:	
Participants received Regorafenib (Stivarga) 160 mg (4 x 40 mg tablets) per os once daily, 3 weeks on therapy followed by 1 week off therapy to comprise a cycle of 4 weeks	
Reporting group title	Placebo first, then Option of Open Label Regorafenib Treatment
Reporting group description:	
Double blind phase: participants received matching Placebo tablets per os once daily, 3 weeks on therapy followed by 1 week off therapy to comprise a cycle of 4 weeks. Open Label phase: participants on placebo who switched to Regorafenib, received Regorafenib 160 mg (4 x 40 mg tablets) per os once daily, 3 weeks on therapy followed by 1 week off therapy to comprise a cycle of 4 weeks.	

Primary: Progression-free Survival

End point title	Progression-free Survival
End point description:	
Progression-free Survival (PFS) was defined as the time from date of randomization to radiological disease progression or death due to any cause, whichever occurs first. PFS was based on central radiological assessment using modified RECIST (Response Evaluation Criteria in Solid Tumors) v.1.1. Progression is defined as at least a 20% increase in the sum of diameters of target lesions taking as reference the smallest sum on study; or unequivocal progression of existing non-target lesions; or appearance of new lesions. Subjects without progression or death at the time of analysis were censored at their last date of tumor evaluation. Results are based on central evaluation.	
End point type	Primary
End point timeframe:	
From randomization of the first subject until approximately 144 progression-free survival events had	

End point values	Regorafenib (Stivarga, BAY73-4506)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	133	66		
Units: Days				
median (confidence interval 95%)	147 (122 to 173)	28 (28 to 32)		

Statistical analyses

Statistical analysis title	Progression-free Survival analysis

Statistical analysis description:

The two treatment groups were compared using a stratified log rank test with a one-sided alpha of 0.01 stratified by (3rd vs 4th-line; and geographical region). The null hypothesis that both treatment arms have the same PFS distribution was tested against the alternative hypothesis that the distribution of PFS in the regorafenib arm is different from the control arm according to a proportional hazards relation between the treatment arms.

Comparison groups	Regorafenib (Stivarga, BAY73-4506) v Placebo
Number of subjects included in analysis	199
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	< 0.000001 [2]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.268
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.185
upper limit	0.388

Notes:

[1] - Hazard ratio and its 95% CI (Confidence Interval) was based on stratified Cox Regression Model

[2] - stratified logrank

Secondary: Overall Survival

End point title	Overall Survival

End point description:

Overall Survival (OS) was defined as the time from date of randomization to death due to any cause. Subjects still alive at the time of analysis were censored at their date of last contact. Median OS was not observed at the time of PFS analysis and first analysis of OS, therefore only the proportion of death events was reported in the results posting system. This approach was maintained for the subsequent updates in the results posting system.

End point type	Secondary

End point timeframe:

From randomization of the first subject until date of database cutoff (08 Jun 2015)

End point values	Regorafenib (Stivarga, BAY73-4506)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	133	66		
Units: Percentage of patients with death				
number (not applicable)	82.0	80.3		

Statistical analyses

Statistical analysis title	Overall survival analysis
Statistical analysis description:	
Hazard ratio and its 95% CI was based on stratified Cox Regression Model	
Comparison groups	Regorafenib (Stivarga, BAY73-4506) v Placebo
Number of subjects included in analysis	199
Analysis specification	Pre-specified
Analysis type	other[3]
P-value	= 0.285777 [4]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.909
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.653
upper limit	1.265

Notes:

[3] - Regorafenib over control. 58 (87.9%) patients in placebo group and 91 (68.4%) patients in regorafenib had started open-label treatment with regorafenib before time of final database cutoff 08 Jun 2015.
[4] - stratified Log Rank

Secondary: Time to Progression (TTP)

End point title	Time to Progression (TTP)

End point description:

Time to progression (TTP) was defined as the time from date of randomization to disease progression (based on central radiological assessment using modified RECIST [Response Evaluation Criteria in Solid Tumors] v.1.1). Progression is defined as at least a 20% increase in the sum of diameters of target lesions taking as reference the smallest sum on study; or unequivocal progression of existing non-target lesions; or appearance of new lesions. Subjects without progression at the time of analysis were censored at their last date of tumor evaluation. Results are based on central evaluation.

End point type	Secondary

End point timeframe:

From randomization of the first subject until until date of database cutoff (26 Jan 2012); study duration approximately 1 year

End point values	Regorafenib (Stivarga, BAY73-4506)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	133	66		
Units: Days				
median (confidence interval 95%)	165 (125 to 174)	28 (28 to 34)		

Statistical analyses

Statistical analysis title	Time to progression analysis
Statistical analysis description: as of the data cutoff date of 26 JAN 2012	
Comparison groups	Regorafenib (Stivarga, BAY73-4506) v Placebo
Number of subjects included in analysis	199
Analysis specification	Pre-specified
Analysis type	superiority[5]
P-value	< 0.001 [6]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.248
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.17
upper limit	0.364

Notes:

[5] - Hazard ratio and its 95% CI was based on stratified Cox Regression Model regorafenib over control. 58 (87.9%) patients in placebo group and 91 (68.4%) patients in regorafenib had started open-label treatment with regorafenib before time of final database cutoff 08 Jun 2015.
[6] - Stratified log rank

Secondary: Tumor Response

End point title	Tumor Response

End point description:

Tumor Response of a subject was defined as the best tumor response (Complete Response [CR: disappearance of all clinical and radiological evidence of tumor (both target and non-target).], Partial Response [PR: at least a 30% decrease in the sum of diameters of target lesions taking as reference the baseline sum, no unequivocal progression of existing non-target lesions, and no appearance of new lesions.], Stable Disease [SD: steady state of disease. Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, no unequivocal progression of existing non-target lesions, and no appearance of new lesions.], or Progressive Disease [PD: at least a 20% increase in the sum of diameters of target lesions taking as reference the smallest sum on study or unequivocal progression of existing non-target lesions, or appearance of new lesions.]) observed during the trial period and assessed according to RECIST v1.1 criteria. Results are based on central evaluation.

End point type	Secondary

End point timeframe:

From randomization of the first subject until date of database cutoff (26 Jan 2012); study duration approximately 1 year

End point values	Regorafenib (Stivarga, BAY73-4506)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	133	66		
Units: Percentage of Participants				
number (confidence interval 95%)				
Complete Response (CR)	0 (0 to 0)	0 (0 to 0)		
Partial Response (PR)	4.5 (1.7 to 9.6)	1.5 (0 to 8.2)		
Stable Disease (SD)	71.4 (63.0 to 78.9)	33.3 (22.2 to 46.0)		
Progressive Disease (PD)	21.1 (14.5 to 29.0)	63.6 (50.9 to 75.1)		
Not Assessable	3.0 (0.8 to 7.5)	1.5 (0 to 8.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Objective response rate

End point title	Objective response rate

End point description:

Objective response rate was defined as the percentage of subjects whose best response was Complete Response (CR: disappearance of all clinical and radiological evidence of tumor (both target and non-target).) or Partial Response (PR: at least a 30% decrease in the sum of diameters of target lesions taking as reference the baseline sum, no unequivocal progression of existing non-target lesions, and no appearance of new lesions.) according to Response Evaluation Criteria in Solid Tumors (RECIST v1.1). Results are based on central evaluation.

End point type	Secondary

End point timeframe:

From randomization of the first subject until date of database cutoff (26 Jan 2012); study duration approximately 1 year.

End point values	Regorafenib (Stivarga, BAY73-4506)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	133	66		
Units: Percentage of Participants				
number (confidence interval 95%)	4.5 (1.7 to 9.6)	1.5 (0.0 to 8.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Disease Control Rate (DCR)

End point title	Disease Control Rate (DCR)

End point description:

Disease Control Rate (DCR) was defined as the percentage of subjects whose best response was Complete Response (CR: disappearance of all clinical and radiological evidence of tumor (both target and non-target).), Partial Response (PR: at least a 30% decrease in the sum of diameters of target lesions taking as reference the baseline sum, no unequivocal progression of existing non-target lesions, and no appearance of new lesions.), or Stable Disease (SD: steady state of disease. Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, no unequivocal progression of existing non-target lesions, and no appearance of new lesions.) according to RECIST v1.1 criteria. SD had to be maintained for at least 12 weeks from the first demonstration of that rating. Results are based on central evaluation.

End point type	Secondary

End point timeframe:

From randomization of the first subject until date of database cutoff (26 Jan 2012); study duration approximately 1 year

End point values	Regorafenib (Stivarga, BAY73-4506)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	133	66		
Units: Percentage of Participants				
number (confidence interval 95%)	52.6 (43.8 to 61.3)	9.1 (3.4 to 18.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DOR)

End point title	Duration of Response (DOR)

End point description:

Duration of Response was defined as the time from date of first response (Complete Response or Partial Response) to the date when Progressive Disease is first documented, or to the date of death, whichever occurs first, according to RECIST v1.1. Subjects still having CR or PR and have not died at the time of analysis were censored at their last date of tumor evaluation. Duration of response defined for responders only, i.e CR or PR. Results are based on central evaluation. “99999” entered in confidence interval (CI) stands for “data cannot calculated because there were too few patients in the data set.” The lower limit of CI in placebo arm (30) was a place-holder, as there was only 1 patient in the data set.

End point type	Secondary

End point timeframe:

From randomization of the first subject until date of database cutoff (26 Jan 2012); study duration approximately 1 year

End point values	Regorafenib (Stivarga, BAY73-4506)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	1		
Units: Days				
median (confidence interval 95%)	99 (42 to 99999)	30 (30 to 99999)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From randomization of the first subject until date of database cutoff (15 Apr 2019).

Adverse event reporting additional description:

At cutoff 26JAN2012 blinded patients were reported in “Regorafenib (DoubleBlindOnly)” and “Placebo (DoubleBlindOnly)”; patients after unblinding were reported in "Placebo, OpenLabelOnly(Switch to Regorafenib)". This safety update (cutoff 15APR2019) was reported in “Treated with Regorafenib at any time” and “Treated with Regorafenib for>1 year”.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.0

Reporting groups

Reporting group title	Regorafenib (Double Blind Only)

Reporting group description:

Participants received Regorafenib (Stivarga) 160 mg (4 x 40 mg tablets) per os once daily, 3 weeks on therapy followed by 1 week off therapy to comprise a cycle of 4 weeks

Reporting group title	Placebo (Double Blind Only)

Reporting group description:

Participants received matching Placebo tablets per os once daily, 3 weeks on therapy followed by 1 week off therapy to comprise a cycle of 4 weeks

Reporting group title	Placebo, Open Label Only (Switch to Regorafenib)

Reporting group description:

Participants switched to Open-label Regorafenib treatment from Placebo. Participants received Regorafenib (Stivarga) 160 mg (4 x 40 mg tablets) per os once daily, 3 weeks

Reporting group title	Treated with Regorafenib at any time

Reporting group description:

Treated with Regorafenib at any time: At any time, participants received Regorafenib (Stivarga) 160 mg (4 x 40 mg tablets) per os once daily, 3 weeks on therapy followed by 1 week off therapy to comprise a cycle of 4 weeks

Reporting group title	Treated with Regorafenib for > 1 year

Reporting group description:

Treated with Regorafenib for > 1 year: For more than a year, participants received Regorafenib (Stivarga) 160 mg (4 x 40 mg tablets) per os once daily, 3 weeks on therapy followed by 1 week off therapy to comprise a cycle of 4 weeks

Serious adverse events	Regorafenib (Double Blind Only)	Placebo (Double Blind Only)	Placebo, Open Label Only (Switch to Regorafenib)
Total subjects affected by serious adverse events			
subjects affected / exposed	23 / 41 (56.10%)	8 / 8 (100.00%)	31 / 58 (53.45%)
number of deaths (all causes)	40	7	47
number of deaths resulting from adverse events	8	3	12
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other			

subjects affected / exposed	1 / 41 (2.44%)	0 / 8 (0.00%)	3 / 58 (5.17%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 3
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Tumor pain			
subjects affected / exposed	0 / 41 (0.00%)	0 / 8 (0.00%)	2 / 58 (3.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 41 (2.44%)	0 / 8 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders - Other			
subjects affected / exposed	0 / 41 (0.00%)	0 / 8 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral ischemia			
subjects affected / exposed	0 / 41 (0.00%)	0 / 8 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thromboembolic event			
subjects affected / exposed	1 / 41 (2.44%)	0 / 8 (0.00%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	0 / 1	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Surgical and medical procedures			
Surgical and medical procedures - Other			
subjects affected / exposed	0 / 41 (0.00%)	0 / 8 (0.00%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Death NOS			

subjects affected / exposed	1 / 41 (2.44%)	2 / 8 (25.00%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 2	0 / 1
Edema limbs			
subjects affected / exposed	0 / 41 (0.00%)	0 / 8 (0.00%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fatigue			
subjects affected / exposed	2 / 41 (4.88%)	1 / 8 (12.50%)	2 / 58 (3.45%)
occurrences causally related to treatment / all	3 / 4	2 / 2	2 / 2
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Fever			
subjects affected / exposed	1 / 41 (2.44%)	0 / 8 (0.00%)	2 / 58 (3.45%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malaise			
subjects affected / exposed	1 / 41 (2.44%)	0 / 8 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Multi-organ failure			
subjects affected / exposed	0 / 41 (0.00%)	0 / 8 (0.00%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Non-cardiac chest pain			
subjects affected / exposed	0 / 41 (0.00%)	1 / 8 (12.50%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions - Other			
subjects affected / exposed	1 / 41 (2.44%)	1 / 8 (12.50%)	2 / 58 (3.45%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Pain			

subjects affected / exposed	1 / 41 (2.44%)	0 / 8 (0.00%)	2 / 58 (3.45%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Adult respiratory distress syndrome			
subjects affected / exposed	0 / 41 (0.00%)	0 / 8 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnea			
subjects affected / exposed	1 / 41 (2.44%)	0 / 8 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			
subjects affected / exposed	0 / 41 (0.00%)	0 / 8 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonitis			
subjects affected / exposed	1 / 41 (2.44%)	0 / 8 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	0 / 41 (0.00%)	0 / 8 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Confusion			
subjects affected / exposed	0 / 41 (0.00%)	0 / 8 (0.00%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mania			
subjects affected / exposed	0 / 41 (0.00%)	1 / 8 (12.50%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Psychiatric disorders - Other			
subjects affected / exposed	1 / 41 (2.44%)	0 / 8 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 41 (0.00%)	0 / 8 (0.00%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 41 (0.00%)	0 / 8 (0.00%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood bilirubin increased			
subjects affected / exposed	0 / 41 (0.00%)	0 / 8 (0.00%)	2 / 58 (3.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Creatinine increased			
subjects affected / exposed	1 / 41 (2.44%)	0 / 8 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
INR increased			
subjects affected / exposed	0 / 41 (0.00%)	0 / 8 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutrophil count decreased			
subjects affected / exposed	0 / 41 (0.00%)	0 / 8 (0.00%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations - Other			
subjects affected / exposed	1 / 41 (2.44%)	0 / 8 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Platelet count decreased			
subjects affected / exposed	0 / 41 (0.00%)	0 / 8 (0.00%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Fracture			
subjects affected / exposed	0 / 41 (0.00%)	0 / 8 (0.00%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hip fracture			
subjects affected / exposed	0 / 41 (0.00%)	0 / 8 (0.00%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Congenital, familial and genetic disorders			
Congenital, familial and genetic disorders - Other			
subjects affected / exposed	0 / 41 (0.00%)	0 / 8 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	0 / 41 (0.00%)	0 / 8 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	0 / 41 (0.00%)	0 / 8 (0.00%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac arrest			
subjects affected / exposed	1 / 41 (2.44%)	0 / 8 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Chest pain - cardiac			

subjects affected / exposed	0 / 41 (0.00%)	0 / 8 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Conduction disorder			
subjects affected / exposed	0 / 41 (0.00%)	0 / 8 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Heart failure			
subjects affected / exposed	0 / 41 (0.00%)	0 / 8 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders - Other			
subjects affected / exposed	0 / 41 (0.00%)	0 / 8 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Amnesia			
subjects affected / exposed	0 / 41 (0.00%)	0 / 8 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoglossal nerve disorder			
subjects affected / exposed	1 / 41 (2.44%)	0 / 8 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intracranial hemorrhage			
subjects affected / exposed	0 / 41 (0.00%)	0 / 8 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders - Other			
subjects affected / exposed	0 / 41 (0.00%)	0 / 8 (0.00%)	2 / 58 (3.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Paresthesia			

subjects affected / exposed	1 / 41 (2.44%)	0 / 8 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reversible posterior leukoencephalopathy syndrome			
subjects affected / exposed	1 / 41 (2.44%)	0 / 8 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Somnolence			
subjects affected / exposed	1 / 41 (2.44%)	0 / 8 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stroke			
subjects affected / exposed	0 / 41 (0.00%)	0 / 8 (0.00%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Transient ischemic attacks			
subjects affected / exposed	0 / 41 (0.00%)	0 / 8 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anemia			
subjects affected / exposed	0 / 41 (0.00%)	0 / 8 (0.00%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Vertigo			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 41 (0.00%)	0 / 8 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Eye disorders - Other			

subjects affected / exposed	0 / 41 (0.00%)	0 / 8 (0.00%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	5 / 41 (12.20%)	0 / 8 (0.00%)	2 / 58 (3.45%)
occurrences causally related to treatment / all	0 / 5	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anal fistula			
subjects affected / exposed	0 / 41 (0.00%)	0 / 8 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ascites			
subjects affected / exposed	3 / 41 (7.32%)	0 / 8 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colonic fistula			
subjects affected / exposed	1 / 41 (2.44%)	0 / 8 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colonic obstruction			
subjects affected / exposed	0 / 41 (0.00%)	0 / 8 (0.00%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colonic perforation			
subjects affected / exposed	0 / 41 (0.00%)	0 / 8 (0.00%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Constipation			
subjects affected / exposed	0 / 41 (0.00%)	0 / 8 (0.00%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhea			

subjects affected / exposed	1 / 41 (2.44%)	0 / 8 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric hemorrhage			
subjects affected / exposed	1 / 41 (2.44%)	0 / 8 (0.00%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Intra-abdominal hemorrhage			
subjects affected / exposed	1 / 41 (2.44%)	0 / 8 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ileus			
subjects affected / exposed	1 / 41 (2.44%)	0 / 8 (0.00%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Lower gastrointestinal hemorrhage			
subjects affected / exposed	1 / 41 (2.44%)	0 / 8 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	0 / 41 (0.00%)	1 / 8 (12.50%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Obstruction gastric			
subjects affected / exposed	0 / 41 (0.00%)	0 / 8 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders - Other			
subjects affected / exposed	1 / 41 (2.44%)	0 / 8 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Peritoneal necrosis			

subjects affected / exposed	1 / 41 (2.44%)	0 / 8 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Retroperitoneal hemorrhage			
subjects affected / exposed	0 / 41 (0.00%)	0 / 8 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal obstruction			
subjects affected / exposed	0 / 41 (0.00%)	0 / 8 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper gastrointestinal hemorrhage			
subjects affected / exposed	0 / 41 (0.00%)	0 / 8 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	0 / 41 (0.00%)	0 / 8 (0.00%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Bile duct stenosis			
subjects affected / exposed	0 / 41 (0.00%)	0 / 8 (0.00%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis			
subjects affected / exposed	0 / 41 (0.00%)	0 / 8 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic failure			
subjects affected / exposed	1 / 41 (2.44%)	0 / 8 (0.00%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 1
Hepatic hemorrhage			

subjects affected / exposed	0 / 41 (0.00%)	0 / 8 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders - Other			
subjects affected / exposed	0 / 41 (0.00%)	1 / 8 (12.50%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Portal vein thrombosis			
subjects affected / exposed	0 / 41 (0.00%)	0 / 8 (0.00%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Rash maculo-papular			
subjects affected / exposed	0 / 41 (0.00%)	0 / 8 (0.00%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	2 / 41 (4.88%)	0 / 8 (0.00%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	0 / 2	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 1	0 / 0	1 / 1
Renal and urinary disorders - Other			
subjects affected / exposed	0 / 41 (0.00%)	0 / 8 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal colic			
subjects affected / exposed	0 / 41 (0.00%)	0 / 8 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary retention			
subjects affected / exposed	1 / 41 (2.44%)	0 / 8 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue			

disorders			
Back pain			
subjects affected / exposed	0 / 41 (0.00%)	0 / 8 (0.00%)	2 / 58 (3.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Generalized muscle weakness			
subjects affected / exposed	0 / 41 (0.00%)	0 / 8 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorder - Other			
subjects affected / exposed	0 / 41 (0.00%)	0 / 8 (0.00%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Muscle weakness right-sided			
subjects affected / exposed	1 / 41 (2.44%)	0 / 8 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Abdominal infection			
subjects affected / exposed	1 / 41 (2.44%)	0 / 8 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Appendicitis			
subjects affected / exposed	0 / 41 (0.00%)	0 / 8 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchial infection			
subjects affected / exposed	0 / 41 (0.00%)	0 / 8 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Catheter related infection			
subjects affected / exposed	0 / 41 (0.00%)	0 / 8 (0.00%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Enterocolitis infectious			
subjects affected / exposed	0 / 41 (0.00%)	0 / 8 (0.00%)	2 / 58 (3.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung infection			
subjects affected / exposed	0 / 41 (0.00%)	0 / 8 (0.00%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations - Other			
subjects affected / exposed	1 / 41 (2.44%)	0 / 8 (0.00%)	4 / 58 (6.90%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Sepsis			
subjects affected / exposed	0 / 41 (0.00%)	0 / 8 (0.00%)	2 / 58 (3.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Upper respiratory infection			
subjects affected / exposed	0 / 41 (0.00%)	0 / 8 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	0 / 41 (0.00%)	0 / 8 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound infection			
subjects affected / exposed	1 / 41 (2.44%)	0 / 8 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Acidosis			
subjects affected / exposed	1 / 41 (2.44%)	0 / 8 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Anorexia			

subjects affected / exposed	1 / 41 (2.44%)	0 / 8 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dehydration			
subjects affected / exposed	0 / 41 (0.00%)	1 / 8 (12.50%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperglycemia			
subjects affected / exposed	0 / 41 (0.00%)	1 / 8 (12.50%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperkalemia			
subjects affected / exposed	1 / 41 (2.44%)	0 / 8 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Treated with Regorafenib at any time	Treated with Regorafenib for > 1 year	
Total subjects affected by serious adverse events			
subjects affected / exposed	103 / 190 (54.21%)	39 / 75 (52.00%)	
number of deaths (all causes)	155	48	
number of deaths resulting from adverse events	33	9	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other			
subjects affected / exposed	6 / 190 (3.16%)	3 / 75 (4.00%)	
occurrences causally related to treatment / all	1 / 6	1 / 3	
deaths causally related to treatment / all	0 / 3	0 / 0	
Tumor pain			
subjects affected / exposed	3 / 190 (1.58%)	1 / 75 (1.33%)	
occurrences causally related to treatment / all	0 / 5	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypertension			

subjects affected / exposed	1 / 190 (0.53%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders - Other			
subjects affected / exposed	1 / 190 (0.53%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Peripheral ischemia			
subjects affected / exposed	1 / 190 (0.53%)	1 / 75 (1.33%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thromboembolic event			
subjects affected / exposed	4 / 190 (2.11%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	3 / 5	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Surgical and medical procedures			
Surgical and medical procedures - Other			
subjects affected / exposed	4 / 190 (2.11%)	2 / 75 (2.67%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Death NOS			
subjects affected / exposed	3 / 190 (1.58%)	2 / 75 (2.67%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 3	0 / 2	
Edema limbs			
subjects affected / exposed	1 / 190 (0.53%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			
subjects affected / exposed	5 / 190 (2.63%)	2 / 75 (2.67%)	
occurrences causally related to treatment / all	5 / 7	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Fever			
subjects affected / exposed	5 / 190 (2.63%)	2 / 75 (2.67%)	
occurrences causally related to treatment / all	0 / 5	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malaise			
subjects affected / exposed	1 / 190 (0.53%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multi-organ failure			
subjects affected / exposed	2 / 190 (1.05%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Non-cardiac chest pain			
subjects affected / exposed	0 / 190 (0.00%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions - Other			
subjects affected / exposed	5 / 190 (2.63%)	3 / 75 (4.00%)	
occurrences causally related to treatment / all	0 / 6	0 / 3	
deaths causally related to treatment / all	0 / 3	0 / 2	
Pain			
subjects affected / exposed	3 / 190 (1.58%)	1 / 75 (1.33%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Adult respiratory distress syndrome			
subjects affected / exposed	1 / 190 (0.53%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnea			
subjects affected / exposed	2 / 190 (1.05%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pleural effusion			
subjects affected / exposed	1 / 190 (0.53%)	1 / 75 (1.33%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	1 / 190 (0.53%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	1 / 190 (0.53%)	1 / 75 (1.33%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Psychiatric disorders			
Confusion			
subjects affected / exposed	1 / 190 (0.53%)	1 / 75 (1.33%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mania			
subjects affected / exposed	0 / 190 (0.00%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders - Other			
subjects affected / exposed	1 / 190 (0.53%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	3 / 190 (1.58%)	1 / 75 (1.33%)	
occurrences causally related to treatment / all	2 / 6	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 190 (0.53%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Blood bilirubin increased			
subjects affected / exposed	3 / 190 (1.58%)	1 / 75 (1.33%)	
occurrences causally related to treatment / all	1 / 3	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Creatinine increased			
subjects affected / exposed	1 / 190 (0.53%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
INR increased			
subjects affected / exposed	1 / 190 (0.53%)	1 / 75 (1.33%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutrophil count decreased			
subjects affected / exposed	1 / 190 (0.53%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations - Other			
subjects affected / exposed	2 / 190 (1.05%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Platelet count decreased			
subjects affected / exposed	1 / 190 (0.53%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Fracture			
subjects affected / exposed	4 / 190 (2.11%)	3 / 75 (4.00%)	
occurrences causally related to treatment / all	0 / 5	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture			
subjects affected / exposed	1 / 190 (0.53%)	1 / 75 (1.33%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Congenital, familial and genetic disorders			
Congenital, familial and genetic disorders - Other			
subjects affected / exposed	1 / 190 (0.53%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	7 / 190 (3.68%)	6 / 75 (8.00%)	
occurrences causally related to treatment / all	2 / 7	2 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	1 / 190 (0.53%)	1 / 75 (1.33%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	1 / 190 (0.53%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Chest pain - cardiac			
subjects affected / exposed	1 / 190 (0.53%)	1 / 75 (1.33%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Conduction disorder			
subjects affected / exposed	1 / 190 (0.53%)	1 / 75 (1.33%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Heart failure			
subjects affected / exposed	1 / 190 (0.53%)	1 / 75 (1.33%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Cardiac disorders - Other			

subjects affected / exposed	1 / 190 (0.53%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Amnesia			
subjects affected / exposed	1 / 190 (0.53%)	1 / 75 (1.33%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglossal nerve disorder			
subjects affected / exposed	1 / 190 (0.53%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intracranial hemorrhage			
subjects affected / exposed	1 / 190 (0.53%)	1 / 75 (1.33%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders - Other			
subjects affected / exposed	2 / 190 (1.05%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Paresthesia			
subjects affected / exposed	1 / 190 (0.53%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reversible posterior leukoencephalopathy syndrome			
subjects affected / exposed	1 / 190 (0.53%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Somnolence			
subjects affected / exposed	1 / 190 (0.53%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stroke			

subjects affected / exposed	2 / 190 (1.05%)	2 / 75 (2.67%)	
occurrences causally related to treatment / all	1 / 2	1 / 2	
deaths causally related to treatment / all	0 / 1	0 / 1	
Transient ischemic attacks			
subjects affected / exposed	2 / 190 (1.05%)	2 / 75 (2.67%)	
occurrences causally related to treatment / all	1 / 2	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anemia			
subjects affected / exposed	2 / 190 (1.05%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Vertigo			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 190 (0.53%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Eye disorders - Other			
subjects affected / exposed	1 / 190 (0.53%)	1 / 75 (1.33%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	9 / 190 (4.74%)	1 / 75 (1.33%)	
occurrences causally related to treatment / all	0 / 10	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal fistula			
subjects affected / exposed	1 / 190 (0.53%)	1 / 75 (1.33%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites			

subjects affected / exposed	3 / 190 (1.58%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colonic fistula			
subjects affected / exposed	1 / 190 (0.53%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colonic obstruction			
subjects affected / exposed	1 / 190 (0.53%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colonic perforation			
subjects affected / exposed	2 / 190 (1.05%)	1 / 75 (1.33%)	
occurrences causally related to treatment / all	4 / 4	2 / 2	
deaths causally related to treatment / all	1 / 1	0 / 0	
Constipation			
subjects affected / exposed	2 / 190 (1.05%)	2 / 75 (2.67%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhea			
subjects affected / exposed	3 / 190 (1.58%)	2 / 75 (2.67%)	
occurrences causally related to treatment / all	4 / 4	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric hemorrhage			
subjects affected / exposed	2 / 190 (1.05%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Intra-abdominal hemorrhage			
subjects affected / exposed	3 / 190 (1.58%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			

subjects affected / exposed	2 / 190 (1.05%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Lower gastrointestinal hemorrhage			
subjects affected / exposed	1 / 190 (0.53%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	2 / 190 (1.05%)	1 / 75 (1.33%)	
occurrences causally related to treatment / all	1 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Obstruction gastric			
subjects affected / exposed	1 / 190 (0.53%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Gastrointestinal disorders - Other			
subjects affected / exposed	1 / 190 (0.53%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Peritoneal necrosis			
subjects affected / exposed	1 / 190 (0.53%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Retroperitoneal hemorrhage			
subjects affected / exposed	1 / 190 (0.53%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	1 / 190 (0.53%)	1 / 75 (1.33%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal hemorrhage			

subjects affected / exposed	1 / 190 (0.53%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	2 / 190 (1.05%)	1 / 75 (1.33%)	
occurrences causally related to treatment / all	1 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Bile duct stenosis			
subjects affected / exposed	2 / 190 (1.05%)	1 / 75 (1.33%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			
subjects affected / exposed	2 / 190 (1.05%)	2 / 75 (2.67%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic failure			
subjects affected / exposed	3 / 190 (1.58%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	2 / 4	0 / 0	
deaths causally related to treatment / all	1 / 2	0 / 0	
Hepatic hemorrhage			
subjects affected / exposed	2 / 190 (1.05%)	1 / 75 (1.33%)	
occurrences causally related to treatment / all	1 / 3	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders - Other			
subjects affected / exposed	2 / 190 (1.05%)	1 / 75 (1.33%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Portal vein thrombosis			
subjects affected / exposed	1 / 190 (0.53%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			

Rash maculo-papular			
subjects affected / exposed	1 / 190 (0.53%)	1 / 75 (1.33%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	4 / 190 (2.11%)	1 / 75 (1.33%)	
occurrences causally related to treatment / all	2 / 5	0 / 1	
deaths causally related to treatment / all	1 / 2	0 / 0	
Renal and urinary disorders - Other			
subjects affected / exposed	3 / 190 (1.58%)	1 / 75 (1.33%)	
occurrences causally related to treatment / all	1 / 4	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 1	
Renal colic			
subjects affected / exposed	1 / 190 (0.53%)	1 / 75 (1.33%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			
subjects affected / exposed	2 / 190 (1.05%)	1 / 75 (1.33%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	2 / 190 (1.05%)	1 / 75 (1.33%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Generalized muscle weakness			
subjects affected / exposed	1 / 190 (0.53%)	1 / 75 (1.33%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorder - Other			

subjects affected / exposed	1 / 190 (0.53%)	1 / 75 (1.33%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscle weakness right-sided			
subjects affected / exposed	1 / 190 (0.53%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abdominal infection			
subjects affected / exposed	2 / 190 (1.05%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
subjects affected / exposed	1 / 190 (0.53%)	1 / 75 (1.33%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchial infection			
subjects affected / exposed	2 / 190 (1.05%)	1 / 75 (1.33%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Catheter related infection			
subjects affected / exposed	1 / 190 (0.53%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis infectious			
subjects affected / exposed	2 / 190 (1.05%)	1 / 75 (1.33%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			
subjects affected / exposed	2 / 190 (1.05%)	1 / 75 (1.33%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations - Other			

subjects affected / exposed	8 / 190 (4.21%)	3 / 75 (4.00%)	
occurrences causally related to treatment / all	0 / 9	0 / 4	
deaths causally related to treatment / all	0 / 1	0 / 1	
Sepsis			
subjects affected / exposed	3 / 190 (1.58%)	1 / 75 (1.33%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 2	0 / 0	
Upper respiratory infection			
subjects affected / exposed	3 / 190 (1.58%)	3 / 75 (4.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 190 (0.53%)	1 / 75 (1.33%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection			
subjects affected / exposed	1 / 190 (0.53%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Acidosis			
subjects affected / exposed	1 / 190 (0.53%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Anorexia			
subjects affected / exposed	1 / 190 (0.53%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	3 / 190 (1.58%)	3 / 75 (4.00%)	
occurrences causally related to treatment / all	2 / 3	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycemia			

subjects affected / exposed	0 / 190 (0.00%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalemia			
subjects affected / exposed	1 / 190 (0.53%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Regorafenib (Double Blind Only)	Placebo (Double Blind Only)	Placebo, Open Label Only (Switch to Regorafenib)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	40 / 41 (97.56%)	7 / 8 (87.50%)	58 / 58 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumor pain			
subjects affected / exposed	1 / 41 (2.44%)	1 / 8 (12.50%)	3 / 58 (5.17%)
occurrences (all)	2	1	4
Vascular disorders			
Hypotension			
subjects affected / exposed	1 / 41 (2.44%)	0 / 8 (0.00%)	1 / 58 (1.72%)
occurrences (all)	1	0	1
Hypertension			
subjects affected / exposed	18 / 41 (43.90%)	3 / 8 (37.50%)	37 / 58 (63.79%)
occurrences (all)	32	3	97
Thromboembolic event			
subjects affected / exposed	0 / 41 (0.00%)	2 / 8 (25.00%)	1 / 58 (1.72%)
occurrences (all)	0	2	1
General disorders and administration site conditions			
Chills			
subjects affected / exposed	1 / 41 (2.44%)	0 / 8 (0.00%)	4 / 58 (6.90%)
occurrences (all)	1	0	4
Edema limbs			
subjects affected / exposed	3 / 41 (7.32%)	3 / 8 (37.50%)	11 / 58 (18.97%)
occurrences (all)	4	3	20

Fatigue			
subjects affected / exposed	18 / 41 (43.90%)	3 / 8 (37.50%)	32 / 58 (55.17%)
occurrences (all)	32	4	83
Fever			
subjects affected / exposed	10 / 41 (24.39%)	1 / 8 (12.50%)	18 / 58 (31.03%)
occurrences (all)	17	1	24
Flu like symptoms			
subjects affected / exposed	1 / 41 (2.44%)	0 / 8 (0.00%)	3 / 58 (5.17%)
occurrences (all)	1	0	3
Localized edema			
subjects affected / exposed	2 / 41 (4.88%)	1 / 8 (12.50%)	3 / 58 (5.17%)
occurrences (all)	2	1	5
Non-cardiac chest pain			
subjects affected / exposed	0 / 41 (0.00%)	0 / 8 (0.00%)	1 / 58 (1.72%)
occurrences (all)	0	0	1
General disorders and administration site conditions - Other			
subjects affected / exposed	1 / 41 (2.44%)	0 / 8 (0.00%)	4 / 58 (6.90%)
occurrences (all)	1	0	5
Pain			
subjects affected / exposed	5 / 41 (12.20%)	1 / 8 (12.50%)	19 / 58 (32.76%)
occurrences (all)	8	1	46
Immune system disorders			
Allergic reaction			
subjects affected / exposed	0 / 41 (0.00%)	0 / 8 (0.00%)	1 / 58 (1.72%)
occurrences (all)	0	0	1
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 41 (2.44%)	1 / 8 (12.50%)	11 / 58 (18.97%)
occurrences (all)	1	1	18
Dyspnea			
subjects affected / exposed	4 / 41 (9.76%)	0 / 8 (0.00%)	7 / 58 (12.07%)
occurrences (all)	6	0	9
Epistaxis			
subjects affected / exposed	0 / 41 (0.00%)	0 / 8 (0.00%)	4 / 58 (6.90%)
occurrences (all)	0	0	6
Hiccups			

subjects affected / exposed	0 / 41 (0.00%)	1 / 8 (12.50%)	0 / 58 (0.00%)
occurrences (all)	0	1	0
Hoarseness			
subjects affected / exposed	8 / 41 (19.51%)	0 / 8 (0.00%)	9 / 58 (15.52%)
occurrences (all)	8	0	11
Pneumonitis			
subjects affected / exposed	0 / 41 (0.00%)	0 / 8 (0.00%)	3 / 58 (5.17%)
occurrences (all)	0	0	3
Voice alteration			
subjects affected / exposed	2 / 41 (4.88%)	1 / 8 (12.50%)	11 / 58 (18.97%)
occurrences (all)	2	1	12
Psychiatric disorders			
Anxiety			
subjects affected / exposed	4 / 41 (9.76%)	0 / 8 (0.00%)	3 / 58 (5.17%)
occurrences (all)	4	0	4
Confusion			
subjects affected / exposed	0 / 41 (0.00%)	1 / 8 (12.50%)	1 / 58 (1.72%)
occurrences (all)	0	1	1
Depression			
subjects affected / exposed	2 / 41 (4.88%)	0 / 8 (0.00%)	2 / 58 (3.45%)
occurrences (all)	2	0	2
Insomnia			
subjects affected / exposed	3 / 41 (7.32%)	1 / 8 (12.50%)	3 / 58 (5.17%)
occurrences (all)	3	1	4
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	4 / 41 (9.76%)	1 / 8 (12.50%)	6 / 58 (10.34%)
occurrences (all)	9	2	15
Alkaline phosphatase increased			
subjects affected / exposed	1 / 41 (2.44%)	1 / 8 (12.50%)	3 / 58 (5.17%)
occurrences (all)	1	1	6
Aspartate aminotransferase increased			
subjects affected / exposed	4 / 41 (9.76%)	2 / 8 (25.00%)	8 / 58 (13.79%)
occurrences (all)	9	2	15
Blood bilirubin increased			

subjects affected / exposed	4 / 41 (9.76%)	1 / 8 (12.50%)	9 / 58 (15.52%)
occurrences (all)	6	3	15
GGT increased			
subjects affected / exposed	0 / 41 (0.00%)	1 / 8 (12.50%)	2 / 58 (3.45%)
occurrences (all)	0	2	2
Lipase increased			
subjects affected / exposed	1 / 41 (2.44%)	0 / 8 (0.00%)	3 / 58 (5.17%)
occurrences (all)	1	0	11
Neutrophil count decreased			
subjects affected / exposed	0 / 41 (0.00%)	0 / 8 (0.00%)	6 / 58 (10.34%)
occurrences (all)	0	0	8
Investigations - Other			
subjects affected / exposed	0 / 41 (0.00%)	0 / 8 (0.00%)	2 / 58 (3.45%)
occurrences (all)	0	0	14
Platelet count decreased			
subjects affected / exposed	1 / 41 (2.44%)	0 / 8 (0.00%)	6 / 58 (10.34%)
occurrences (all)	5	0	25
White blood cell decreased			
subjects affected / exposed	0 / 41 (0.00%)	0 / 8 (0.00%)	2 / 58 (3.45%)
occurrences (all)	0	0	2
Weight gain			
subjects affected / exposed	0 / 41 (0.00%)	1 / 8 (12.50%)	2 / 58 (3.45%)
occurrences (all)	0	1	3
Weight loss			
subjects affected / exposed	4 / 41 (9.76%)	2 / 8 (25.00%)	11 / 58 (18.97%)
occurrences (all)	5	2	20
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 41 (0.00%)	1 / 8 (12.50%)	1 / 58 (1.72%)
occurrences (all)	0	1	1
Dysgeusia			
subjects affected / exposed	2 / 41 (4.88%)	0 / 8 (0.00%)	4 / 58 (6.90%)
occurrences (all)	2	0	4
Headache			
subjects affected / exposed	4 / 41 (9.76%)	0 / 8 (0.00%)	11 / 58 (18.97%)
occurrences (all)	4	0	21

Paresthesia			
subjects affected / exposed	0 / 41 (0.00%)	0 / 8 (0.00%)	3 / 58 (5.17%)
occurrences (all)	0	0	5
Peripheral sensory neuropathy			
subjects affected / exposed	5 / 41 (12.20%)	0 / 8 (0.00%)	4 / 58 (6.90%)
occurrences (all)	7	0	8
Somnolence			
subjects affected / exposed	0 / 41 (0.00%)	1 / 8 (12.50%)	0 / 58 (0.00%)
occurrences (all)	0	1	0
Blood and lymphatic system disorders			
Anemia			
subjects affected / exposed	4 / 41 (9.76%)	0 / 8 (0.00%)	11 / 58 (18.97%)
occurrences (all)	7	0	25
Blood and lymphatic system disorders - Other			
subjects affected / exposed	0 / 41 (0.00%)	0 / 8 (0.00%)	2 / 58 (3.45%)
occurrences (all)	0	0	9
Ear and labyrinth disorders			
Hearing impaired			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 41 (2.44%)	0 / 8 (0.00%)	1 / 58 (1.72%)
occurrences (all)	1	0	1
Ear and labyrinth disorders - Other			
subjects affected / exposed	0 / 41 (0.00%)	0 / 8 (0.00%)	4 / 58 (6.90%)
occurrences (all)	0	0	4
Eye disorders			
Blurred vision			
subjects affected / exposed	0 / 41 (0.00%)	0 / 8 (0.00%)	2 / 58 (3.45%)
occurrences (all)	0	0	2
Eye disorders - Other			
subjects affected / exposed	0 / 41 (0.00%)	0 / 8 (0.00%)	1 / 58 (1.72%)
occurrences (all)	0	0	1
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	14 / 41 (34.15%)	0 / 8 (0.00%)	16 / 58 (27.59%)
occurrences (all)	18	0	23
Ascites			

subjects affected / exposed	2 / 41 (4.88%)	1 / 8 (12.50%)	2 / 58 (3.45%)
occurrences (all)	2	1	2
Bloating			
subjects affected / exposed	0 / 41 (0.00%)	0 / 8 (0.00%)	1 / 58 (1.72%)
occurrences (all)	0	0	1
Constipation			
subjects affected / exposed	10 / 41 (24.39%)	5 / 8 (62.50%)	16 / 58 (27.59%)
occurrences (all)	14	6	30
Diarrhea			
subjects affected / exposed	15 / 41 (36.59%)	1 / 8 (12.50%)	24 / 58 (41.38%)
occurrences (all)	20	1	67
Dyspepsia			
subjects affected / exposed	4 / 41 (9.76%)	1 / 8 (12.50%)	6 / 58 (10.34%)
occurrences (all)	4	2	9
Dry mouth			
subjects affected / exposed	5 / 41 (12.20%)	0 / 8 (0.00%)	5 / 58 (8.62%)
occurrences (all)	5	0	6
Flatulence			
subjects affected / exposed	4 / 41 (9.76%)	0 / 8 (0.00%)	3 / 58 (5.17%)
occurrences (all)	4	0	3
Mucositis oral			
subjects affected / exposed	14 / 41 (34.15%)	2 / 8 (25.00%)	21 / 58 (36.21%)
occurrences (all)	18	3	48
Nausea			
subjects affected / exposed	9 / 41 (21.95%)	3 / 8 (37.50%)	18 / 58 (31.03%)
occurrences (all)	12	4	33
Gastrointestinal disorders - Other			
subjects affected / exposed	4 / 41 (9.76%)	0 / 8 (0.00%)	4 / 58 (6.90%)
occurrences (all)	4	0	7
Stomach pain			
subjects affected / exposed	0 / 41 (0.00%)	0 / 8 (0.00%)	2 / 58 (3.45%)
occurrences (all)	0	0	2
Vomiting			
subjects affected / exposed	10 / 41 (24.39%)	3 / 8 (37.50%)	12 / 58 (20.69%)
occurrences (all)	11	5	24
Skin and subcutaneous tissue disorders			

Alopecia			
subjects affected / exposed	7 / 41 (17.07%)	0 / 8 (0.00%)	21 / 58 (36.21%)
occurrences (all)	9	0	26
Dry skin			
subjects affected / exposed	2 / 41 (4.88%)	0 / 8 (0.00%)	2 / 58 (3.45%)
occurrences (all)	3	0	3
Erythema multiforme			
subjects affected / exposed	1 / 41 (2.44%)	0 / 8 (0.00%)	1 / 58 (1.72%)
occurrences (all)	1	0	3
Erythroderma			
subjects affected / exposed	0 / 41 (0.00%)	0 / 8 (0.00%)	4 / 58 (6.90%)
occurrences (all)	0	0	5
Hyperhidrosis			
subjects affected / exposed	0 / 41 (0.00%)	1 / 8 (12.50%)	2 / 58 (3.45%)
occurrences (all)	0	2	2
Skin and subcutaneous tissue disorders - Other			
subjects affected / exposed	3 / 41 (7.32%)	0 / 8 (0.00%)	7 / 58 (12.07%)
occurrences (all)	3	0	10
Pain of skin			
subjects affected / exposed	0 / 41 (0.00%)	0 / 8 (0.00%)	1 / 58 (1.72%)
occurrences (all)	0	0	1
Palmar-plantar erythrodysesthesia syndrome			
subjects affected / exposed	17 / 41 (41.46%)	1 / 8 (12.50%)	39 / 58 (67.24%)
occurrences (all)	37	1	151
Pruritus			
subjects affected / exposed	4 / 41 (9.76%)	1 / 8 (12.50%)	7 / 58 (12.07%)
occurrences (all)	4	2	8
Rash acneiform			
subjects affected / exposed	2 / 41 (4.88%)	0 / 8 (0.00%)	3 / 58 (5.17%)
occurrences (all)	2	0	3
Rash maculo-papular			
subjects affected / exposed	6 / 41 (14.63%)	0 / 8 (0.00%)	8 / 58 (13.79%)
occurrences (all)	7	0	10
Renal and urinary disorders			

Hematuria			
subjects affected / exposed	1 / 41 (2.44%)	0 / 8 (0.00%)	3 / 58 (5.17%)
occurrences (all)	1	0	3
Renal and urinary disorders - Other			
subjects affected / exposed	3 / 41 (7.32%)	0 / 8 (0.00%)	0 / 58 (0.00%)
occurrences (all)	3	0	0
Proteinuria			
subjects affected / exposed	0 / 41 (0.00%)	0 / 8 (0.00%)	6 / 58 (10.34%)
occurrences (all)	0	0	11
Urinary frequency			
subjects affected / exposed	0 / 41 (0.00%)	0 / 8 (0.00%)	2 / 58 (3.45%)
occurrences (all)	0	0	2
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	4 / 41 (9.76%)	0 / 8 (0.00%)	6 / 58 (10.34%)
occurrences (all)	4	0	6
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 41 (2.44%)	0 / 8 (0.00%)	4 / 58 (6.90%)
occurrences (all)	1	0	7
Back pain			
subjects affected / exposed	2 / 41 (4.88%)	1 / 8 (12.50%)	4 / 58 (6.90%)
occurrences (all)	2	1	6
Bone pain			
subjects affected / exposed	0 / 41 (0.00%)	0 / 8 (0.00%)	1 / 58 (1.72%)
occurrences (all)	0	0	3
Flank pain			
subjects affected / exposed	0 / 41 (0.00%)	0 / 8 (0.00%)	1 / 58 (1.72%)
occurrences (all)	0	0	1
Generalized muscle weakness			
subjects affected / exposed	1 / 41 (2.44%)	1 / 8 (12.50%)	4 / 58 (6.90%)
occurrences (all)	1	1	7
Myalgia			
subjects affected / exposed	5 / 41 (12.20%)	3 / 8 (37.50%)	10 / 58 (17.24%)
occurrences (all)	5	3	17
Neck pain			

subjects affected / exposed	0 / 41 (0.00%)	1 / 8 (12.50%)	0 / 58 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal and connective tissue disorder - Other			
subjects affected / exposed	1 / 41 (2.44%)	0 / 8 (0.00%)	4 / 58 (6.90%)
occurrences (all)	1	0	5
Pain in extremity			
subjects affected / exposed	5 / 41 (12.20%)	1 / 8 (12.50%)	7 / 58 (12.07%)
occurrences (all)	5	2	15
Infections and infestations			
Bronchial infection			
subjects affected / exposed	0 / 41 (0.00%)	0 / 8 (0.00%)	4 / 58 (6.90%)
occurrences (all)	0	0	4
Infections and infestations - Other			
subjects affected / exposed	2 / 41 (4.88%)	0 / 8 (0.00%)	5 / 58 (8.62%)
occurrences (all)	3	0	7
Rash pustular			
subjects affected / exposed	2 / 41 (4.88%)	0 / 8 (0.00%)	2 / 58 (3.45%)
occurrences (all)	2	0	17
Sinusitis			
subjects affected / exposed	1 / 41 (2.44%)	0 / 8 (0.00%)	1 / 58 (1.72%)
occurrences (all)	1	0	1
Skin infection			
subjects affected / exposed	0 / 41 (0.00%)	0 / 8 (0.00%)	3 / 58 (5.17%)
occurrences (all)	0	0	4
Tooth infection			
subjects affected / exposed	0 / 41 (0.00%)	0 / 8 (0.00%)	1 / 58 (1.72%)
occurrences (all)	0	0	1
Upper respiratory infection			
subjects affected / exposed	0 / 41 (0.00%)	0 / 8 (0.00%)	9 / 58 (15.52%)
occurrences (all)	0	0	12
Urinary tract infection			
subjects affected / exposed	2 / 41 (4.88%)	0 / 8 (0.00%)	2 / 58 (3.45%)
occurrences (all)	3	0	4
Metabolism and nutrition disorders			

Anorexia			
subjects affected / exposed	15 / 41 (36.59%)	3 / 8 (37.50%)	20 / 58 (34.48%)
occurrences (all)	21	5	42
Dehydration			
subjects affected / exposed	0 / 41 (0.00%)	1 / 8 (12.50%)	5 / 58 (8.62%)
occurrences (all)	0	1	5
Hypoalbuminemia			
subjects affected / exposed	2 / 41 (4.88%)	0 / 8 (0.00%)	3 / 58 (5.17%)
occurrences (all)	2	0	3
Hypocalcemia			
subjects affected / exposed	1 / 41 (2.44%)	0 / 8 (0.00%)	3 / 58 (5.17%)
occurrences (all)	2	0	8
Hypokalemia			
subjects affected / exposed	0 / 41 (0.00%)	0 / 8 (0.00%)	12 / 58 (20.69%)
occurrences (all)	0	0	18
Hyponatremia			
subjects affected / exposed	0 / 41 (0.00%)	2 / 8 (25.00%)	3 / 58 (5.17%)
occurrences (all)	0	2	4
Hypophosphatemia			
subjects affected / exposed	1 / 41 (2.44%)	0 / 8 (0.00%)	1 / 58 (1.72%)
occurrences (all)	1	0	1
Hypercalcemia			
subjects affected / exposed	0 / 41 (0.00%)	1 / 8 (12.50%)	3 / 58 (5.17%)
occurrences (all)	0	1	3
Hyperglycemia			
subjects affected / exposed	1 / 41 (2.44%)	0 / 8 (0.00%)	5 / 58 (8.62%)
occurrences (all)	3	0	5
Hyperuricemia			
subjects affected / exposed	1 / 41 (2.44%)	1 / 8 (12.50%)	2 / 58 (3.45%)
occurrences (all)	1	1	2

Non-serious adverse events	Treated with Regorafenib at any time	Treated with Regorafenib for > 1 year	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	189 / 190 (99.47%)	75 / 75 (100.00%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			

Tumor pain			
subjects affected / exposed	7 / 190 (3.68%)	2 / 75 (2.67%)	
occurrences (all)	9	2	
Vascular disorders			
Hypotension			
subjects affected / exposed	7 / 190 (3.68%)	4 / 75 (5.33%)	
occurrences (all)	8	5	
Hypertension			
subjects affected / exposed	124 / 190 (65.26%)	62 / 75 (82.67%)	
occurrences (all)	697	552	
Thromboembolic event			
subjects affected / exposed	6 / 190 (3.16%)	5 / 75 (6.67%)	
occurrences (all)	7	5	
General disorders and administration site conditions			
Chills			
subjects affected / exposed	11 / 190 (5.79%)	8 / 75 (10.67%)	
occurrences (all)	19	16	
Edema limbs			
subjects affected / exposed	33 / 190 (17.37%)	17 / 75 (22.67%)	
occurrences (all)	72	53	
Fatigue			
subjects affected / exposed	104 / 190 (54.74%)	46 / 75 (61.33%)	
occurrences (all)	251	137	
Fever			
subjects affected / exposed	52 / 190 (27.37%)	25 / 75 (33.33%)	
occurrences (all)	83	46	
Flu like symptoms			
subjects affected / exposed	18 / 190 (9.47%)	14 / 75 (18.67%)	
occurrences (all)	22	17	
Localized edema			
subjects affected / exposed	8 / 190 (4.21%)	5 / 75 (6.67%)	
occurrences (all)	10	7	
Non-cardiac chest pain			
subjects affected / exposed	7 / 190 (3.68%)	6 / 75 (8.00%)	
occurrences (all)	8	7	
General disorders and administration site conditions - Other			

subjects affected / exposed	10 / 190 (5.26%)	5 / 75 (6.67%)	
occurrences (all)	11	6	
Pain			
subjects affected / exposed	55 / 190 (28.95%)	29 / 75 (38.67%)	
occurrences (all)	115	73	
Immune system disorders			
Allergic reaction			
subjects affected / exposed	4 / 190 (2.11%)	4 / 75 (5.33%)	
occurrences (all)	4	4	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	27 / 190 (14.21%)	15 / 75 (20.00%)	
occurrences (all)	44	32	
Dyspnea			
subjects affected / exposed	22 / 190 (11.58%)	11 / 75 (14.67%)	
occurrences (all)	32	16	
Epistaxis			
subjects affected / exposed	10 / 190 (5.26%)	7 / 75 (9.33%)	
occurrences (all)	15	10	
Hiccups			
subjects affected / exposed	0 / 190 (0.00%)	0 / 75 (0.00%)	
occurrences (all)	0	0	
Hoarseness			
subjects affected / exposed	42 / 190 (22.11%)	17 / 75 (22.67%)	
occurrences (all)	71	36	
Pneumonitis			
subjects affected / exposed	5 / 190 (2.63%)	4 / 75 (5.33%)	
occurrences (all)	5	4	
Voice alteration			
subjects affected / exposed	28 / 190 (14.74%)	14 / 75 (18.67%)	
occurrences (all)	32	17	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	9 / 190 (4.74%)	4 / 75 (5.33%)	
occurrences (all)	10	5	
Confusion			

subjects affected / exposed	2 / 190 (1.05%)	0 / 75 (0.00%)	
occurrences (all)	2	0	
Depression			
subjects affected / exposed	10 / 190 (5.26%)	4 / 75 (5.33%)	
occurrences (all)	11	5	
Insomnia			
subjects affected / exposed	21 / 190 (11.05%)	14 / 75 (18.67%)	
occurrences (all)	22	15	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	20 / 190 (10.53%)	4 / 75 (5.33%)	
occurrences (all)	41	10	
Alkaline phosphatase increased			
subjects affected / exposed	11 / 190 (5.79%)	3 / 75 (4.00%)	
occurrences (all)	21	4	
Aspartate aminotransferase increased			
subjects affected / exposed	23 / 190 (12.11%)	6 / 75 (8.00%)	
occurrences (all)	58	24	
Blood bilirubin increased			
subjects affected / exposed	22 / 190 (11.58%)	7 / 75 (9.33%)	
occurrences (all)	52	27	
GGT increased			
subjects affected / exposed	4 / 190 (2.11%)	1 / 75 (1.33%)	
occurrences (all)	4	1	
Lipase increased			
subjects affected / exposed	6 / 190 (3.16%)	3 / 75 (4.00%)	
occurrences (all)	19	14	
Neutrophil count decreased			
subjects affected / exposed	13 / 190 (6.84%)	6 / 75 (8.00%)	
occurrences (all)	25	12	
Investigations - Other			
subjects affected / exposed	14 / 190 (7.37%)	10 / 75 (13.33%)	
occurrences (all)	49	28	
Platelet count decreased			

subjects affected / exposed	15 / 190 (7.89%)	10 / 75 (13.33%)	
occurrences (all)	46	34	
White blood cell decreased			
subjects affected / exposed	6 / 190 (3.16%)	4 / 75 (5.33%)	
occurrences (all)	17	15	
Weight gain			
subjects affected / exposed	3 / 190 (1.58%)	2 / 75 (2.67%)	
occurrences (all)	4	3	
Weight loss			
subjects affected / exposed	40 / 190 (21.05%)	22 / 75 (29.33%)	
occurrences (all)	72	44	
Nervous system disorders			
Dizziness			
subjects affected / exposed	6 / 190 (3.16%)	6 / 75 (8.00%)	
occurrences (all)	16	16	
Dysgeusia			
subjects affected / exposed	17 / 190 (8.95%)	9 / 75 (12.00%)	
occurrences (all)	19	11	
Headache			
subjects affected / exposed	37 / 190 (19.47%)	23 / 75 (30.67%)	
occurrences (all)	72	55	
Paresthesia			
subjects affected / exposed	11 / 190 (5.79%)	9 / 75 (12.00%)	
occurrences (all)	19	13	
Peripheral sensory neuropathy			
subjects affected / exposed	16 / 190 (8.42%)	6 / 75 (8.00%)	
occurrences (all)	22	7	
Somnolence			
subjects affected / exposed	0 / 190 (0.00%)	0 / 75 (0.00%)	
occurrences (all)	0	0	
Blood and lymphatic system disorders			
Anemia			
subjects affected / exposed	35 / 190 (18.42%)	17 / 75 (22.67%)	
occurrences (all)	77	35	
Blood and lymphatic system disorders - Other			

subjects affected / exposed	6 / 190 (3.16%)	4 / 75 (5.33%)	
occurrences (all)	17	9	
Ear and labyrinth disorders			
Hearing impaired			
alternative assessment type: Systematic			
subjects affected / exposed	7 / 190 (3.68%)	5 / 75 (6.67%)	
occurrences (all)	7	5	
Ear and labyrinth disorders - Other			
subjects affected / exposed	7 / 190 (3.68%)	4 / 75 (5.33%)	
occurrences (all)	7	4	
Eye disorders			
Blurred vision			
subjects affected / exposed	7 / 190 (3.68%)	7 / 75 (9.33%)	
occurrences (all)	7	7	
Eye disorders - Other			
subjects affected / exposed	6 / 190 (3.16%)	4 / 75 (5.33%)	
occurrences (all)	6	4	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	62 / 190 (32.63%)	26 / 75 (34.67%)	
occurrences (all)	122	60	
Ascites			
subjects affected / exposed	6 / 190 (3.16%)	1 / 75 (1.33%)	
occurrences (all)	8	3	
Bloating			
subjects affected / exposed	7 / 190 (3.68%)	6 / 75 (8.00%)	
occurrences (all)	10	9	
Constipation			
subjects affected / exposed	63 / 190 (33.16%)	28 / 75 (37.33%)	
occurrences (all)	101	52	
Diarrhea			
subjects affected / exposed	96 / 190 (50.53%)	53 / 75 (70.67%)	
occurrences (all)	353	281	
Dyspepsia			
subjects affected / exposed	19 / 190 (10.00%)	11 / 75 (14.67%)	
occurrences (all)	39	30	

Dry mouth			
subjects affected / exposed	15 / 190 (7.89%)	5 / 75 (6.67%)	
occurrences (all)	16	6	
Flatulence			
subjects affected / exposed	10 / 190 (5.26%)	5 / 75 (6.67%)	
occurrences (all)	11	6	
Mucositis oral			
subjects affected / exposed	81 / 190 (42.63%)	38 / 75 (50.67%)	
occurrences (all)	174	111	
Nausea			
subjects affected / exposed	61 / 190 (32.11%)	32 / 75 (42.67%)	
occurrences (all)	110	66	
Gastrointestinal disorders - Other			
subjects affected / exposed	17 / 190 (8.95%)	11 / 75 (14.67%)	
occurrences (all)	21	15	
Stomach pain			
subjects affected / exposed	7 / 190 (3.68%)	5 / 75 (6.67%)	
occurrences (all)	7	5	
Vomiting			
subjects affected / exposed	48 / 190 (25.26%)	21 / 75 (28.00%)	
occurrences (all)	85	54	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	62 / 190 (32.63%)	33 / 75 (44.00%)	
occurrences (all)	84	49	
Dry skin			
subjects affected / exposed	13 / 190 (6.84%)	7 / 75 (9.33%)	
occurrences (all)	15	8	
Erythema multiforme			
subjects affected / exposed	10 / 190 (5.26%)	7 / 75 (9.33%)	
occurrences (all)	17	12	
Erythroderma			
subjects affected / exposed	9 / 190 (4.74%)	6 / 75 (8.00%)	
occurrences (all)	11	6	
Hyperhidrosis			

subjects affected / exposed	6 / 190 (3.16%)	4 / 75 (5.33%)	
occurrences (all)	11	9	
Skin and subcutaneous tissue disorders - Other			
subjects affected / exposed	27 / 190 (14.21%)	17 / 75 (22.67%)	
occurrences (all)	41	28	
Pain of skin			
subjects affected / exposed	9 / 190 (4.74%)	6 / 75 (8.00%)	
occurrences (all)	39	36	
Palmar-plantar erythrodysesthesia syndrome			
subjects affected / exposed	126 / 190 (66.32%)	58 / 75 (77.33%)	
occurrences (all)	666	455	
Pruritus			
subjects affected / exposed	20 / 190 (10.53%)	10 / 75 (13.33%)	
occurrences (all)	27	15	
Rash acneiform			
subjects affected / exposed	12 / 190 (6.32%)	7 / 75 (9.33%)	
occurrences (all)	12	7	
Rash maculo-papular			
subjects affected / exposed	32 / 190 (16.84%)	16 / 75 (21.33%)	
occurrences (all)	71	26	
Renal and urinary disorders			
Hematuria			
subjects affected / exposed	7 / 190 (3.68%)	3 / 75 (4.00%)	
occurrences (all)	9	3	
Renal and urinary disorders - Other			
subjects affected / exposed	10 / 190 (5.26%)	4 / 75 (5.33%)	
occurrences (all)	12	5	
Proteinuria			
subjects affected / exposed	23 / 190 (12.11%)	9 / 75 (12.00%)	
occurrences (all)	58	21	
Urinary frequency			
subjects affected / exposed	7 / 190 (3.68%)	4 / 75 (5.33%)	
occurrences (all)	8	5	
Endocrine disorders			

Hypothyroidism			
subjects affected / exposed	39 / 190 (20.53%)	25 / 75 (33.33%)	
occurrences (all)	50	32	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	14 / 190 (7.37%)	8 / 75 (10.67%)	
occurrences (all)	20	14	
Back pain			
subjects affected / exposed	21 / 190 (11.05%)	14 / 75 (18.67%)	
occurrences (all)	29	20	
Bone pain			
subjects affected / exposed	5 / 190 (2.63%)	5 / 75 (6.67%)	
occurrences (all)	9	9	
Flank pain			
subjects affected / exposed	5 / 190 (2.63%)	4 / 75 (5.33%)	
occurrences (all)	5	4	
Generalized muscle weakness			
subjects affected / exposed	6 / 190 (3.16%)	3 / 75 (4.00%)	
occurrences (all)	14	11	
Myalgia			
subjects affected / exposed	34 / 190 (17.89%)	17 / 75 (22.67%)	
occurrences (all)	76	49	
Neck pain			
subjects affected / exposed	2 / 190 (1.05%)	1 / 75 (1.33%)	
occurrences (all)	2	1	
Musculoskeletal and connective tissue disorder - Other			
subjects affected / exposed	14 / 190 (7.37%)	10 / 75 (13.33%)	
occurrences (all)	17	12	
Pain in extremity			
subjects affected / exposed	28 / 190 (14.74%)	17 / 75 (22.67%)	
occurrences (all)	51	37	
Infections and infestations			
Bronchial infection			
subjects affected / exposed	11 / 190 (5.79%)	9 / 75 (12.00%)	
occurrences (all)	12	10	
Infections and infestations - Other			

subjects affected / exposed	21 / 190 (11.05%)	13 / 75 (17.33%)	
occurrences (all)	39	26	
Rash pustular			
subjects affected / exposed	13 / 190 (6.84%)	10 / 75 (13.33%)	
occurrences (all)	49	42	
Sinusitis			
subjects affected / exposed	6 / 190 (3.16%)	5 / 75 (6.67%)	
occurrences (all)	6	5	
Skin infection			
subjects affected / exposed	6 / 190 (3.16%)	4 / 75 (5.33%)	
occurrences (all)	7	4	
Tooth infection			
subjects affected / exposed	6 / 190 (3.16%)	5 / 75 (6.67%)	
occurrences (all)	6	5	
Upper respiratory infection			
subjects affected / exposed	26 / 190 (13.68%)	21 / 75 (28.00%)	
occurrences (all)	41	36	
Urinary tract infection			
subjects affected / exposed	12 / 190 (6.32%)	6 / 75 (8.00%)	
occurrences (all)	17	9	
Metabolism and nutrition disorders			
Anorexia			
subjects affected / exposed	77 / 190 (40.53%)	32 / 75 (42.67%)	
occurrences (all)	134	72	
Dehydration			
subjects affected / exposed	6 / 190 (3.16%)	4 / 75 (5.33%)	
occurrences (all)	8	6	
Hypoalbuminemia			
subjects affected / exposed	9 / 190 (4.74%)	2 / 75 (2.67%)	
occurrences (all)	10	2	
Hypocalcemia			
subjects affected / exposed	9 / 190 (4.74%)	4 / 75 (5.33%)	
occurrences (all)	15	4	
Hypokalemia			
subjects affected / exposed	20 / 190 (10.53%)	13 / 75 (17.33%)	
occurrences (all)	31	22	

Hyponatremia			
subjects affected / exposed	8 / 190 (4.21%)	2 / 75 (2.67%)	
occurrences (all)	11	2	
Hypophosphatemia			
subjects affected / exposed	10 / 190 (5.26%)	5 / 75 (6.67%)	
occurrences (all)	13	7	
Hypercalcemia			
subjects affected / exposed	4 / 190 (2.11%)	4 / 75 (5.33%)	
occurrences (all)	4	4	
Hyperglycemia			
subjects affected / exposed	13 / 190 (6.84%)	9 / 75 (12.00%)	
occurrences (all)	18	10	
Hyperuricemia			
subjects affected / exposed	7 / 190 (3.68%)	2 / 75 (2.67%)	
occurrences (all)	7	2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
09 February 2011	a global amendment, was to modify and clarify RECIST v1.1 for GIST tumor evaluation, give patients who were screen failures one more opportunity to be screened for potential study enrollment, implement clarifications (primarily in study procedures) and to correct minor errors or omissions.
26 July 2011	provided specific procedures that must be followed to monitor liver function; changed the frequency of safety assessments during Cycle 5 and Cycle 6; implemented clarifications; and corrected minor errors or omissions.
27 September 2011	a global amendment increased the number of PFS events required for analysis of the primary efficacy endpoint, and indicated that because of the increased current number of randomized patients, the number of survival events for final analysis would also be increased (by the same ratio as the number of PFS events) due to the over recruitment. Also, if the study results supported a positive benefit/risk assessment for regorafenib following primary endpoint analysis, Amendment 3 offered those patients currently on placebo the opportunity to receive regorafenib through open label treatment on this study. In addition, editorial changes and corrections were made.
30 September 2014	a global amendment, was to revise and clarify the study procedures to be performed after data cutoff for the final OS analysis, since efficacy assessments were no longer necessary, but subjects who are benefiting from treatment will have continuing access to study drug.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Overall survival results are confounded by the fact that 85% of the participants initially randomized to placebo switched to open-label regorafenib.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/23177515

http://www.ncbi.nlm.nih.gov/pubmed/24957256

http://www.ncbi.nlm.nih.gov/pubmed/25655899